

EXHIBIT E

Guidance for Industry

Animal Models — Essential Elements to Address Efficacy Under the Animal Rule

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Rosemary Roberts, CDER, at 301-796-2210 or the Office of Communications, Training, and Manufacturers Assistance (CBER), 301-827-1800 or 800-835-4709.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**January 2009
Pharm/Tox**

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

Animal Models — Essential Elements to Address Efficacy Under the Animal Rule

*Office of Training and Communications
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov*

<http://www.fda.gov/cder/guidance/index.htm>

and/or

*Office of Communication, Training, and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
<http://www.fda.gov/cber/guidelines.htm>.*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**January 2009
Pharm/Tox**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	4
II.	BACKGROUND	5
III.	ANIMAL RULE CONSIDERATIONS	5
IV.	DISCUSSION OF ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL ...	7
A.	Characteristics of CBRN Agent that Influence the Disease or Condition	7
1.	<i>The Challenge Agent.....</i>	7
2.	<i>Pathogenic Determinants.....</i>	8
3.	<i>Route of Exposure</i>	8
4.	<i>Quantification of Exposure.....</i>	8
B.	Host Susceptibility and Response to Etiologic Agent	8
C.	Natural History of Disease: Pathophysiologic Comparability	9
1.	<i>Time to Onset of Disease/Condition.....</i>	10
2.	<i>Time Course of Progression of Disease/Condition.....</i>	10
3.	<i>Manifestations (signs and symptoms).....</i>	10
D.	Trigger for Intervention	11
E.	Characterization of Medical Intervention	11
1.	<i>Product Class.....</i>	11
2.	<i>Mechanism of Action.....</i>	12
3.	<i>In vitro Activity</i>	12
4.	<i>Activity in Disease/Condition of Similar Pathophysiology.....</i>	12
5.	<i>Pharmacokinetics (PK) in Unaffected Animals/Humans</i>	12
6.	<i>PK/PD (Pharmacokinetics/Pharmacodynamics) in Affected Animals/Humans</i>	12
7.	<i>PK Interactions with Medical Products Likely to Be Used Concomitantly</i>	13
8.	<i>Synergy or Antagonism of Medical Products Likely to Be Used in Combination</i>	13
F.	Design Considerations for Animal Efficacy Studies	13
1.	<i>Endpoints</i>	14
2.	<i>Timing of intervention</i>	14
3.	<i>Route of Administration</i>	15
4.	<i>Dosing Regimen</i>	15
V.	HUMAN SAFETY INFORMATION.....	16
VI.	ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL	16
ATTACHMENT A:	ACRONYMS AND ABBREVIATIONS	18
REFERENCES.....		19

Contains Nonbinding Recommendations

Draft — Not for Implementation

1
2
Guidance for Industry¹

3
4
Animal Models — Essential Elements to Address
5 **Efficacy Under the Animal Rule**

6
7
8 *This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current*
9 *thinking on this topic. It does not create or confer any rights for or on any person and does not operate*
10 *to bind FDA or the public. You can use an alternative approach if the approach satisfies the*
11 *requirements of the applicable statutes and regulations. If you want to discuss an alternative approach,*
12 *contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate*
13 *FDA staff, call the appropriate number listed on the title page of this guidance.*

16
17
I. INTRODUCTION

18 This guidance provides information to potential sponsors (industry, academia, and government)
19 on the development of animal models to study efficacy. The guidance focuses on the
20 identification of the critical characteristics (essential data elements) of an animal model to be
21 addressed when developing drug or biological products for approval or licensure, respectively,
22 under the Animal Rule (see 21 CFR 314.600 for drugs; 21 CFR 601.90 for biological products).

23
24
25 This guidance does not address:

- 26 • The preclinical pharmacology/toxicology studies necessary for early drug or biological
27 product development
28 • The details of study design and conduct for either animal efficacy studies or human safety
29 studies
30 • The development of animal models for other purposes, such as for assessment of
31 toxicology
32 • The threshold for determining that human efficacy studies are not ethical and/or not
33 feasible

34
35 FDA's guidance documents, including this guidance, do not establish legally enforceable
36 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
37 be viewed only as recommendations, unless specific regulatory or statutory requirements are
38 cited. The use of the word *should* in Agency guidances means that something is suggested or
39 recommended, but not required.

¹ This guidance has been prepared by the Animal Model Characterization Working Group in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

Contains Nonbinding Recommendations

Draft — Not for Implementation

41

42 **II. BACKGROUND**

43
44 FDA's regulations concerning the approval of new drugs or biological products when human
45 efficacy studies are neither ethical nor feasible are known as "the Animal Rule" (21 CFR
46 314.600 for drugs; 21 CFR 601.90 for biological products). The Animal Rule states that in
47 selected circumstances, when it is neither ethical nor feasible to conduct human efficacy studies,
48 FDA may grant marketing approval based on adequate and well-controlled animal studies when
49 the results of those studies establish that the drug or biological product is reasonably likely to
50 produce clinical benefit in humans. Demonstration of the product's safety in humans is still
51 necessary (see section V.).

52

53 The purpose of this guidance is to identify the critical characteristics of an animal model that
54 should be addressed when efficacy of the product under development will be established under
55 the Animal Rule.

56

57 The critical characteristics discussed in section IV identify the essential elements to be
58 considered and fully explored as part of the development of an animal model. All elements may
59 not be achievable for each etiologic agent² and intervention³ being studied. Early and frequent
60 interactions between FDA and the sponsor are recommended to discuss these elements and any
61 issues encountered by the sponsor. Current FDA requirements for establishing the safety of a
62 product in humans continue to apply. Although the discussion in this guidance touches on
63 clinical safety, it is not meant to address all requirements for assurance of human safety.

64

65

66 **III. ANIMAL RULE CONSIDERATIONS**

67

68 To develop an animal model to demonstrate efficacy, the sponsor should obtain information on
69 the natural history of the disease or condition in both humans and animals, on the etiologic agent,
70 and on the proposed intervention. Data from the human experience with the etiologic agent
71 and/or with the intervention, if available, may support applicability of the animal model.

72

73 The Animal Rule states that FDA can rely on the evidence from animal studies to provide
74 substantial evidence of effectiveness only when:

75

- 76 1. There is a reasonably well-understood pathophysiological mechanism of the toxicity of
77 the (chemical, biological, radiological, or nuclear) substance and its prevention or
78 substantial reduction by the product
- 79 2. The effect is demonstrated in more than one animal species expected to react with a
80 response predictive for humans, unless the effect is demonstrated in a single animal

² For this document the terms *agent*, *threat agent*, or *etiologic agent* refer to lethal or permanently disabling toxic chemical, biological, radiological or nuclear (CBRN) substances regarding which efficacy studies in humans are neither ethical nor feasible. The term *challenge agent* refers to the CBRN material used in the animal studies.

³ The terms *treatment* and *therapy* refer to any intervention that prevents or mitigates the toxicity of these etiologic agents.

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 81 species that represents a sufficiently well-characterized animal model⁴ for predicting the
82 response in humans
83 3. The animal study endpoint is clearly related to the desired benefit in humans, generally
84 the enhancement of survival or prevention of major morbidity
85 4. The data or information on the (pharmac) kinetics and pharmacodynamics of the
86 product or other relevant data or information, in animals and humans, allows selection of
87 an effective dose in humans
88 (21 CFR 314.610(a)(1)-(4); 21 CFR 601.91(a)(1)-(4))
89

90 If these criteria are met, it is reasonable to expect the effectiveness of the product in animals to
91 be a reliable indicator of its effectiveness in humans.
92

93 The Animal Rule allows approval based on a single animal species, if the animal model is
94 sufficiently well-characterized; however the usual expectation is that efficacy will be
95 demonstrated in more than one species. In order to support approval based on one animal
96 species, in general more than one efficacy study using that species should be conducted to
97 demonstrate reproducibility of the results.
98

99 Data from animal studies to demonstrate dose-response and to support the dose selected for the
100 animal efficacy studies are expected as is the case for traditional product development. Sponsors
101 of products approved for other indications may be asked to provide additional nonclinical and/or
102 clinical data to support approval/licensure of the proposed product for the indication under
103 consideration.
104

105 If another regulatory pathway to approval (i.e., one using human data) is feasible and ethical, that
106 pathway must be used (21 CFR 314.600 and 601.90). Although the Animal Rule allows
107 development of products that would otherwise not have any route to approval, the rule reflects
108 the Agency's recognition that many treatments that appeared effective in animals have not
109 proved to be effective in humans. Consequently, developing animal models that will yield
110 efficacy results that can be expected to be predictive for humans is challenging. The animal
111 studies must be adequate and well-controlled (21 CFR 314.610 and 601.91), and should use the
112 pertinent features of an adequate and well-controlled clinical study, such as a detailed protocol
113 with randomization and adequate blinding and a statistical plan as described in 21 CFR 314.126.
114

115 Early and frequent interactions between FDA and the sponsor are recommended to discuss the
116 applicability of the Animal Rule and specific areas of concern, as well as to enable the review of,
117 and comment on, protocols prior to study initiation. FDA may seek Advisory Committee
118 consultation before approval and/or early in the development process to discuss whether the
119 concept of using certain animal data to support efficacy is reasonable.
120

121 All studies intended to support approval under the Animal Rule must be carried out under the
122 procedures and controls outlined in FDA's Good Laboratory Practice (GLP) for Nonclinical
123 Laboratory Studies regulations (21 CFR Part 58). FDA recognizes that conforming to GLP
124 regulations in the conduct of studies on CBRN agents may present challenges. Such issues and

⁴ A "sufficiently well-characterized animal model" is one for which the model has been adequately evaluated for its responsiveness.

Contains Nonbinding Recommendations

Draft — Not for Implementation

125 their possible impact on study results and conclusions, should be discussed with the review
126 division prior to conduct of the studies. In addition, the studies must comply with the Animal
127 Welfare Act (7 U.S.C. 2131). For certain infectious agents, sponsors must adhere to the Select
128 Agent Rule⁵ and should comply with standards on the use of Biosafety Level (BSL) laboratory
129 facilities.⁶

130
131 The animal efficacy studies conducted to support approval under the Animal Rule are likely to
132 use a significant number of animals. Sponsors should submit detailed protocols (see 21 CFR
133 312.23(a)(6)) and provide for frequent monitoring throughout the study period. FDA strongly
134 encourages sponsors to submit a development plan and to communicate frequently with the
135 Agency when developing products under the Animal Rule. The protocols for the animal efficacy
136 studies should be discussed with FDA, with sufficient time for FDA review and comment, prior
137 to the study being conducted.

138
139
140 **IV. DISCUSSION OF ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL**

141
142 This section provides further information on the Table, Essential Data Elements of an Animal
143 Model, found in section VI.

144
145 **A. Characteristics of CBRN Agent that Influence the Disease or Condition**

146
147 Some characteristics of the specific chemical, biological, radiological, and/or nuclear (CBRN)
148 agent that influence the disease or condition under study include: the challenge agent, pathogenic
149 determinants, the route of exposure, and quantification of exposure.

150
151 *1. The Challenge Agent*

152
153 The challenge agent used in animal studies generally should be identical to the etiologic
154 agent that causes the human disease. The purity of the challenge preparation should be
155 documented when appropriate. If the challenge agent is different from the etiologic agent
156 known to cause human disease, the sponsor should provide justification for the use of this
157 challenge agent and explain why, when used in the proposed animal model, it should be
158 considered suitable for establishing effectiveness of the intervention in humans. For
159 example, for an animal efficacy study to support approval of a radiation countermeasure,
160 a sponsor may not be able to predict the actual radiation exposure that would follow a
161 nuclear detonation or the subsequent fallout. In such a case, the sponsor should provide a
162 detailed explanation of the appropriateness of the type of radiation and dose used in the
163 study and its relevance to the clinical situation. FDA strongly recommends that the
164 scientific approach under consideration be discussed with FDA prior to the start of the
165 animal studies.

⁵ See Select Agent Rule (42 CFR Parts 72 & 73) available at http://www.cdc.gov/od/sap/final_rule.htm.

⁶ See 5th Edition of Biosafety in Microbiological and Biomedical Laboratories (BMBL), available at <http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

167

168 2. *Pathogenic Determinants*

169

170 It should be demonstrated that the pathogenic determinants of disease in the animal
171 model are similar to those understood for humans. Pathogenic determinants can include
172 toxin production, target organs or enzyme systems, or type of radiation. For example,
173 although mice and guinea pigs are susceptible to *Bacillus anthracis*, the pathogenesis and
174 mechanism of toxicity are different from those in humans, so that these rodent species
175 may not be appropriate efficacy models for anthrax.⁷ Animal species that are not
176 susceptible to the agent, or do not demonstrate the endpoint of interest (i.e., potential for
177 mortality or major morbidity that might be reduced or prevented by sufficiently effective
178 interventions) are not suitable for the efficacy studies.

179

180 3. *Route of Exposure*

181

182 In general, the animal models developed should use a route of exposure to the challenge
183 agent that is the same as the anticipated human exposure route. This is especially
184 important for conditions for which the route of exposure is directly related to
185 pathogenesis. For example, human infection with *Yersinia pestis* through flea bite, the
186 intravenous (IV) route, or aerosol exposure results in the development of bubonic,
187 septicemic, or pneumonic plague, respectively. If a sponsor is proposing a route of
188 exposure to the etiologic agent in animals that is different from what is expected in
189 humans, adequate scientific justification should be provided. FDA strongly recommends
190 that if such an approach is being considered, it should be discussed with FDA before the
191 start of the animal studies.

192

193 4. *Quantification of Exposure*

194

195 Reliable quantification and reproducibility of the challenge dose should be demonstrated.
196 When appropriate, the sponsor should describe the scalar relationship of the animal dose
197 to that anticipated in human disease. If large differences are observed, then potential
198 implications for interpretation of comparative pathogenesis, pathophysiology, and study
199 results should be discussed with FDA. Standardization of the challenge dose may be a
200 consideration in the future to ensure robust evaluation of data in the determination of
201 effectiveness.

202

203 **B. Host Susceptibility and Response to Etiologic Agent**

204

205 The animal model chosen for development should be susceptible to the threat agent. FDA
206 recognizes there may be species differences. For example, an animal species being used to study
207 efficacy for a radiation countermeasure may require a different threshold of radiation exposure to
208 develop acute radiation syndrome, but the animal species may still be appropriate for study if the
209 resulting illness and course are similar in the animal species and humans. However, if this
210 threshold differs greatly from the human threshold, the suitability of the animal model may be

⁷ Leffel, E.K. and Pitt, L.M., Anthrax. In *Biodefense: Research Methodology and Animal Models*. Swarentgen, J.R. ed. Boca Raton, FL. CRC Press, 2006, 77-93.

Contains Nonbinding Recommendations

Draft -- Not for Implementation

211 called into question. The factor that determines differences in susceptibility to the threat agent
212 should be described to the best extent possible (e.g., see the discussion of pyridostigmine and
213 soman in section E.2).

214
215 The response to the etiologic agent (resulting illness or injury) manifested by the animal species
216 exposed to that agent should be similar to the illness or injury seen in humans. For example,
217 mustard gas typically produces extensive blistering to exposed human skin. If the animal species
218 evaluated does not have blistering as a prominent feature of exposure to mustard gas, it is
219 unlikely that this animal model would be acceptable to the Agency. If the sponsor believes that
220 such a model is supportive to the study of its investigational drug, the model should be discussed
221 with the Agency and a justification should be provided

222
223 **C. Natural History of Disease: Pathophysiologic Comparability**

224
225 The natural history of disease in animals and in humans should be characterized, compared, and
226 discussed with the Agency before the sponsor initiates intervention studies in animals. In some
227 instances, use of several different models in the same development plan can be considered.
228 Experimental parameters may need to be modified to create a condition that more closely mimics
229 the disease in humans. For example, variola virus causes human smallpox, and humans are the
230 only known natural host. Nonhuman primate animal models that have been studied using variola
231 virus as the challenge agent require a large inoculum, and often the IV route of administration is
232 used. FDA recommends that compounds found to be active in vitro against orthopoxviruses be
233 studied in several animal models using multiple different orthopoxviruses initially. Based on
234 data from initial studies and availability of suitably characterized models, the next step may be to
235 assess the appropriateness of additional study in an animal model using variola.⁸ Sponsors who
236 plan to use an animal model that involves exposure to a challenge agent that is different from the
237 known etiologic agent in humans should discuss this with the Agency along with their planned
238 protocols and any major differences in, or limitations of, the animal model.

239
240 When comparing the disease in animals with the disease in humans, sponsors should include
241 time to onset of disease/condition; time course of progression of disease; and manifestations, that
242 is, signs and symptoms (severity, progression, clinical and pathologic features, laboratory
243 parameters, the extent of organ involvement, morbidity, and outcome of disease). A single
244 animal model may not reflect the entire spectrum of human disease. The time to onset of
245 disease, progression of disease, and the manifestations/outcome can be influenced by many
246 factors, including concentration and type of etiologic agent, virulence or lethal potential of the
247 etiologic agent, route of exposure, and other host factors including immune status.

⁸ See FDA's draft guidance for industry *Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention*. Once finalized this guidance will represent the Agency's thinking on this topic.
Also, we update guidances periodically. To make sure you have the most recent version of a guidance, check the appropriate (CDER or CBER) guidance Web site, listed on the second title page of the guidance.

Contains Nonbinding Recommendations

Draft — Not for Implementation

249

1. Time to Onset of Disease/Condition

250

The time to onset of disease/condition in animals should be reasonably similar to that in humans. Factors such as strain of the infective microorganism, route of exposure, and/or the level of exposure (i.e., concentration of the chemical, biological, radiological, or other etiologic agent) can influence time to disease/condition onset.

255

2. Time Course of Progression of Disease/Condition

256

The progression of the disease/condition in animals should be similar to that of the disease in humans to allow for observation of the effects of intervention. For example, hamsters challenged with anthrax have an extremely rapid disease progression. Thus, this species is not useful for testing the efficacy of products for the treatment of anthrax in humans. Furthermore, the clinical course of disease in the animal may be more rapid than that in the human as a result of experimental conditions, such as the route of exposure (e.g., an IV route of exposure may alter many characteristics including the time course of disease). The change in the clinical course may result in making disease recognition, intervention, and assessment of outcome more difficult. Showing the effect of an intervention may be more challenging when the time between onset of disease and death is short.

269

3. Manifestations (signs and symptoms)

270

The disease manifestations, including clinical signs and their known time course, laboratory parameters, histopathology, gross pathology, and the outcome (morbidity or mortality), should be compared between untreated animals and untreated humans (e.g., historical information). Differences should be clearly noted and explained based on the understanding of the pathophysiologic differences between the species, with due acknowledgment of the limitations that may arise where this level of understanding is limited. Because certain disease manifestations in humans (e.g., fever and shortness of breath) may be difficult to discern in animals through clinical observation, a sponsor may need to use more refined techniques, such as telemetry, to evaluate affected animals. Animals in the natural history studies as well as animals in the efficacy studies should be observed with greater frequency over the entire course of the day than would be typical of most nonclinical (pharmacology/toxicology) animal studies. This is especially true when the primary endpoint is mortality and animals are being evaluated in the context of prospectively-defined euthanasia criteria. With a mortality endpoint, animal welfare and sample integrity need to be addressed. Sample integrity (e.g., cultures, histology) may be compromised if not obtained just prior to or immediately after death or euthanasia. Study results may be influenced by the criteria used. Study personnel should be blinded to treatment and should follow observation and euthanasia criteria to minimize the possibility of unnecessary suffering of moribund animals.⁹

271

272

⁹Refer to Animal Welfare Act (7 U.S.C. 2131).

Contains Nonbinding Recommendations

Draft — Not for Implementation

292 **D. Trigger for Intervention**

293
294 Identification of the trigger for intervention in the animal studies is critical to defining the timing
295 of the intervention. Because animals cannot simulate the health-seeking behavior manifested by
296 humans, the trigger for intervention should be accurately defined in the animal model. If signs
297 and symptoms in the animal model closely resemble those in humans, these can serve as the
298 trigger for intervention when they are recognized in the individual animal. However, in the
299 absence of disease-defining manifestations, certain biological parameters should be used to
300 identify the time for initiation of treatment if they are known to be relevant to the diagnosis of
301 human disease and if a relationship to the likely diagnostic process and timing in human use of
302 the product can be shown. For example, presence of bacteremia has been used in some efficacy
303 studies in humans for initiation of intervention with antimicrobial drug products.¹⁰ The utility of
304 biological parameters/biomarkers should be demonstrated, including an analysis of the time
305 course of the appearance of the biomarkers in animals and the onset of disease and availability of
306 diagnostic information in humans.

307
308 When a biomarker is used as a trigger for intervention in animal studies, both the assay
309 methodology for the biomarker and its performance characteristics should be adequately
310 characterized. The materials and methods for the assay, as well as the raw data and results from
311 the actual testing, should be provided for FDA review. Summary data are not sufficient.
312 Sponsors are encouraged to initiate early discussion with FDA regarding the utility of the chosen
313 triggers for intervention, particularly when the signs and symptoms of disease in the animal
314 differ from those in humans.

315 **E. Characterization of Medical Intervention**

316
317 Efficacy studies should reflect the expected clinical use and indication. A particular dosage form
318 may not be suitable for the proposed indication, so the product's dosage form should be
319 considered in planning the development of the product. For example, an oral dosage form is
320 preferred for postexposure prophylaxis for large populations, while an IV dosage form may be
321 necessary for seriously ill patients. If the product is already approved for human use, there may
322 be information on which to base the expected dose and regimen, but if there is no approved
323 human use, the animal result will need to be translated for human use, generally requiring some
324 PK/PD assessment. The following specific information should be submitted on the product and
325 its characteristics in humans and in animals.

326 *1. Product Class*

327
328 The product's therapeutic class should be identified. Information that is available about
329 other members of the class can be used to help identify potential animal models and
330 predict/evaluate safety and efficacy issues in the proposed animal model.

¹⁰ Refer to package insert for Cubicin, NDA No. 021572, accessible at Drugs@FDA:
<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

334

2. *Mechanism of Action*

335

336 Understanding the mechanism of action may help to identify specific safety and efficacy
337 issues in the proposed animal model and to identify what additional studies should be
338 performed. The animal studies to support the approval of pyridostigmine as a
339 pretreatment for exposure to the nerve agent soman highlight the importance of
340 understanding the mechanism of action of the drug and host factors in each animal
341 species evaluated. Pretreatment with pyridostigmine was shown to decrease the lethality
342 of soman in rhesus monkeys. However, pretreatment with pyridostigmine produced
343 small and inconsistent effects on mortality in studies using rats, mice, and rabbits. The
344 effect of pyridostigmine was masked in these latter species because of high serum levels
345 of the enzyme carboxylesterase, which eliminates soman from the blood and makes these
346 species naturally highly resistant to the nerve agent. Rhesus monkeys and humans have
347 little or no carboxylesterase. To elucidate the mechanism of pyridostigmine and bridge
348 the data to the human experience, a study was conducted in rats pretreated with
349 pyridostigmine as well as a carboxylesterase inhibitor prior to exposure to soman. In this
350 study, pyridostigmine demonstrated a mortality benefit in the rats similar to that seen in
351 the rhesus monkeys.

352

353 3. *In vitro Activity*

354

355 Understanding the in vitro activity of the product will supplement known information on
356 the mechanism of action and provide early screening information.

357

358 4. *Activity in Disease/Condition of Similar Pathophysiology*

359

360 If a candidate product is targeted at a common pathway in the pathophysiologic cascade,
361 information may be available on the candidate product's use for diseases that possess a
362 similar pathway. For example, information for a product approved for the treatment of
363 neutropenia secondary to chemotherapy in cancer patients may provide useful data to
364 support studying this product for the reduction of mortality in patients with neutropenia
365 secondary to acute radiation syndrome. This information on the related condition,
366 although not required, lends further support to the candidate product's efficacy for the
367 indication to be studied.

368

369 5. *Pharmacokinetics (PK) in Unaffected Animals/Humans*

370

371 PK studies should be done in unaffected animals and humans to characterize the PK
372 profile in each and to propose dosing regimens that provide comparable drug exposures
373 in the animals and humans. Early interaction with FDA is critical to justify and establish
374 the appropriate dosing regimen for the pivotal animal studies.

375

376 6. *PK/PD (Pharmacokinetics/Pharmacodynamics) in Affected Animals/Humans*

377

378 PK information in affected animals should be compared to PK information obtained from
379 unaffected animals to establish whether the pathophysiology of a disease affects the PK

Contains Nonbinding Recommendations

Draft — Not for Implementation

380 (e.g., changes in metabolic parameters may alter the pharmacokinetics). Measures of
381 treatment response (PD measurements such as clinical outcome or exploratory
382 biomarkers) should be proposed for discussion based on both animal studies and any
383 available human information. If a candidate product has been used in humans for other
384 indications, PK/PD information for the alternate indications may be supportive. It should
385 be noted that the animal model may not predict specific disease/drug interactions. Such
386 interactions may not be observed until the disease is treated in humans, reinforcing the
387 critical need for postmarket clinical studies in the event of human disease.

388

389 7. *PK Interactions with Medical Products Likely to Be Used Concomitantly*

390

391 The absorption, distribution, metabolism, and excretion (ADME)^{11, 12} of a candidate
392 product should be studied and understood.¹³ The sponsor, with knowledge of the ADME
393 of the investigational product, should discuss with FDA other medical products that are
394 likely to be co-administered based on the clinical scenario. Potential combinations
395 should be considered for interaction studies that may affect the PK of either product. For
396 example, if a candidate drug is metabolized via the cytochrome P450 system, safety or
397 efficacy of the candidate drug could be compromised by the concomitant use of
398 cytochrome P450 inhibitors or inducers. Such drug/drug interactions should be
399 evaluated.

400

401 8. *Synergy or Antagonism of Medical Products Likely to Be Used in Combination*

402

403 Candidate products should be evaluated within the context that reflects anticipated
404 clinical use. The sponsor, in consultation with FDA, should consider other products that
405 are likely to be used and evaluate whether the activity of either product, when used in
406 combination, is affected (i.e., synergy or antagonism). Examples of potential interactions
407 include drug/drug interactions and drug/vaccine interactions. For example, it should be
408 known whether the use of an anthrax antitoxin monoclonal will have an effect on the
409 activity of the antimicrobials used for the treatment of disseminated anthrax disease. This
410 potential interaction should therefore be evaluated in the animal model. This information
411 is especially important when the therapeutic intervention is expected to include more than
412 one medical product.

413

414 **F. Design Considerations for Animal Efficacy Studies**

415

416 Assessment of efficacy in animals should be robust. Adequate and well-controlled animal
417 efficacy studies, with endpoints that demonstrate substantial clinical benefit, generally the
418 enhancement of survival or prevention of major morbidity, are required. The time course of
419 observation should be optimized to assess the true treatment effect. At a minimum, placebo-

¹¹ See guidance for industry: *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro*.

¹² See guidance for industry: *Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling*.

¹³ Biodistribution and elimination should be studied for products that are not biologically amenable to traditional ADME measures (e.g., many biologics such as vaccines, and cell and gene therapies).

Contains Nonbinding Recommendations

Draft — Not for Implementation

420 controlled animal studies should be performed. If a product approved for the same indication is
421 available, it should be used as an active comparator in addition to the investigational drug and
422 placebo arms. The study should also be blinded to the extent feasible; any situation in which
423 study staff might become aware of treatment assignments should be discussed with FDA in
424 advance in view of the potential for major effects on study interpretability. Animals of both
425 sexes should be included. FDA recognizes that there are significant supply constraints on using
426 mature or older animals of certain animal species. The issue of the age and the immune status of
427 the animals used in efficacy studies as compared to the intended human population should be
428 addressed by the sponsor, when relevant. Study procedures should be uniformly applied to all
429 study groups, and potential bias should be reduced by prespecifying the criteria for euthanasia
430 and discussing their potential effects on interpretation of results.

431
432 Studies should be designed to mimic the clinical scenario and achieve meaningful outcomes
433 comparable to the endpoints desired in humans. In some instances, supportive care should be
434 administered to the animals as part of the study design. In such cases, demonstration of a
435 product's benefit over supportive care (i.e., supportive care plus investigational drug arm should
436 be demonstrated to be superior to the supportive care plus placebo arm) will be necessary for
437 approval or licensure. Early discussion between the sponsor and the review division regarding
438 the type, timing, and choice of supportive care to be administered is highly recommended.

439
440 In addition to the design characteristics already discussed in this section, the following
441 parameters should also be addressed in the study protocols:

442
443 1. *Endpoints*

444
445 The product studied in the animal model should demonstrate a beneficial effect analogous
446 to the intended outcome in humans. Primary study endpoints, which should be
447 specifically discussed with the review division, generally are the enhancement of survival
448 or prevention of major morbidity. The dose response for these endpoints should be
449 explored fully and established. Although secondary endpoints can provide useful
450 information about the animal model and the activity of the product as studied in the
451 animal model, ordinarily, only primary endpoints can serve as the basis of approval.

452
453 2. *Timing of intervention*

454
455 The time to initiate intervention should support the specific indication sought for a
456 product. If the intent is to develop the product for a treatment indication, intervention
457 before disease is established may overestimate the effect that is likely to be seen in
458 humans and may indeed show an effect when none would be seen in humans. A
459 reasonable understanding of the disease course and a trigger for intervention defined by
460 the natural history studies will be needed to design the animal efficacy studies for a
461 treatment indication; it is important to establish the relationship of time after exposure to
462 effectiveness. With this information, the timing for intervention can be defined, thus
463 differentiating postexposure prophylaxis from treatment. A product to be used for
464 postexposure prophylaxis should be administered within a reasonable window after
465 exposure to the threat agent, but before onset of disease, with a time relationship that is

Contains Nonbinding Recommendations

Draft — Not for Implementation

466 adequately justified with respect to administration of the product to humans. Proposals
467 for pre-exposure prophylaxis should be described and discussed in advance on a case-by-
468 case basis.

469

470 3. *Route of Administration*

471

472 The route of administration should reflect the indication being sought and the anticipated
473 clinical scenario, such as mass casualty. For example, if a large number of people were
474 exposed to anthrax, an oral dosage form would be preferred over an injectable for
475 postexposure prophylaxis. It may be important to study multiple routes.

476

477 4. *Dosing Regimen*

478

479 Drugs, monoclonals, and small therapeutic proteins:

480

481 The determination of the dosing regimen should rely on sufficient PK and PD data or
482 other relevant product information in animals and/or humans. The goals should be to (a)
483 determine a regimen in animals that is safe and effective for the indication studied; (b)
484 determine the corresponding exposure (i.e., AUC, Cmax) in animals that is yielded by
485 that dosing regimen; and (c) calculate a dosing regimen in humans that will give an
486 equivalent exposure to that seen in the animal. This will enable initial extrapolation from
487 a dosing regimen found to be efficacious in the animal model to one expected to produce
488 a similar benefit in humans, assuming similar exposure-response relationships. Different
489 dosing regimens in animals and humans may be needed to provide equivalent exposure to
490 the product and thus should be discussed with the Agency.

491

492 Vaccines:

493

494 The goal should be to develop a regimen that provides a protective immune response and
495 that is safe. For vaccines, the dose(s) used in the animal should induce an immune
496 response that allows for appropriate extrapolation of the animal protection data to humans
497 based on solid scientific principles. A shorter dosing interval between inoculations as
498 compared to the proposed clinical dosing interval may be acceptable with appropriate
499 scientific justification.

500

501 In summary, the indication being sought drives the study design. The desired outcomes of the
502 study (i.e., product's effect) should be determined early and carefully factored into the study
503 design to ensure that the study meets both scientific and regulatory objectives. The Agency
504 recommends that study protocols be prepared and submitted to FDA with enough time for FDA
505 to review the protocols and provide feedback to the sponsor before the animal studies are
506 initiated. The sponsor can submit these protocols (i.e., the adequate and well-controlled animal
507 efficacy studies) with a request for review under the Special Protocol Assessment (SPA)
508 provisions.¹⁴

¹⁴ See guidance for industry: *Special Protocol Assessment*.

Contains Nonbinding Recommendations

Draft — Not for Implementation

509

V. HUMAN SAFETY INFORMATION

510

511 The body of available human safety data, including data from the product's evaluation and use in
512 other indications, is a critical component of any product's development plan and influences the
513 risk/benefit considerations. FDA may ask for additional human safety trials to complete the
514 safety profile of the product. Healthy human volunteers should be enlisted when there is no
515 known significant risk in the administration of the product. If the risk is significant, study in a
516 patient population with a similar disease should be considered if a population can be identified
517 for which the risk/benefit balance of the study is appropriate. Sponsors should propose selection
518 and justification of the appropriate study population in advance for FDA review and feedback.
519

520

521 The size of the required clinical safety database depends on many factors. Existing safety data
522 would generally be satisfactory for products that are already marketed for another indication
523 and known to have an acceptable safety profile in the populations that would receive the product
524 for the new indication. When the new indication requires a longer duration of use or higher
525 dose, additional safety data must be obtained (21 CFR 314.50(d)(5)(vi)). The type of indication
526 being sought is another factor. For example, a product that will be used as prophylaxis in large
527 numbers of people should have a larger safety database than a product developed for treatment of
528 patients who are symptomatic with a disease of known high mortality. In prophylaxis scenarios,
529 it is likely that some proportion of humans will receive the product without having been exposed
530 to the threat agent. An adequate safety database is needed to reduce the risk of serious harm in a
531 healthy population.

532

533 The timing and design of clinical safety studies should be coordinated with exploration of the
534 efficacious dose and regimen in animals, in order to plan adequate studies to characterize the
535 safety of the intended human dose, formulation, route of administration, and duration of use.
536 Preclinical safety information should guide the choice of additional safety assessments of interest
537 in the human safety studies. This is particularly useful for products with no prior human safety
538 data, or when the anticipated human dosing regimen has not been previously studied or
539 approved.

540

541

VI. ESSENTIAL DATA ELEMENTS OF AN ANIMAL MODEL

542

543

544 The essential data elements for the development and evaluation of animal models are listed in the
545 table below. These elements serve as a guide. They may be modified or revised as new scientific
546 information relevant to the condition under study becomes available. Early and frequent
547 interactions between the sponsor and FDA are critical for feedback on proposals and appropriate
548 discussion of uncertainties and the risk/benefit balance.

549

Contains Nonbinding Recommendations

Draft — Not for Implementation

550
551

Table: Essential Data Elements of an Animal Model

DATA ELEMENTS	Animal(s)	Human
A. Characteristics of the CBRN Agent that Influence the Disease or Condition		
1. The challenge agent		
2. Pathogenic determinants		
3. Route of exposure		
4. Quantification of exposure		
B. Host Susceptibility and Response to Etiologic Agent		
C. Natural History of Disease: Pathophysiologic Comparability		
1. Time to onset of disease/condition		
2. Time course of progression of disease/condition		
3. Manifestations (signs and symptoms)		
D. Trigger for Intervention		
E. Characterization of the Medical Intervention		
1. Product class		
2. Mechanism of action		
3. In vitro activity		
4. Activity in disease/condition of similar pathophysiology		
5. PK in unaffected animals/humans		
6. PK/PD in affected animals/humans		
7. PK interactions with medical products likely to be used concomitantly		
8. Synergy or antagonism of medical products likely to be used in combination		
F. Design Considerations for Animal Efficacy Studies		
1. Endpoints		
2. Timing of intervention		
3. Route of administration		
4. Dosing regimen		
HUMAN SAFETY INFORMATION		

552

Contains Nonbinding Recommendations

Draft — Not for Implementation

ATTACHMENT A: ACRONYMS AND ABBREVIATIONS	
553	ADME
554	Absorption, distribution, metabolism, and excretion
555	AUC
556	Area under plasma concentration-time curve from zero to infinity
557	BSL
558	Biosafety Level
559	CBER
560	Center for Biologics Evaluation and Research
561	CBRN
562	Chemical, Biological, Radiological, or Nuclear
563	CDER
564	Center for Drug Evaluation and Research
565	Cmax
566	Maximum (peak) plasma drug concentration after single dose administration
567	FDA
568	Food and Drug Administration
569	GLP
570	Good Laboratory Practices
571	IV
572	Intravenous
573	PD
574	Pharmacodynamics
575	PK
576	Pharmacokinetics
577	SPA
578	Special Protocol Assessment
579	

Contains Nonbinding Recommendations

Draft — Not for Implementation

580

581

582

583 21 CFR, Part 58. Good Laboratory Practice for Nonclinical Laboratory Studies (accessible at
584 <http://www.nal.usda.gov/awic/legislat/21cfr97.htm>).

585

586 42 CFR, Parts 72 and 73. “Possession, Use and Transfer of Select Agents and Toxins,” (CDC)
587 *Federal Register* 70 (March 18, 2005): 13293 – 13325.
588 (accessible at http://www.cdc.gov/od/sap/final_rule.htm)

589

590 FDA, “New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness
591 of New Drugs When Human Efficacy Studies Are Not Ethical and Feasible,” *Federal Register*
592 67 (31 May 2002): 37988-37998.

593

594 FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and
595 Research, guidance for industry, *Drug Interaction Studies – Study Design, Data Analysis, and*
596 *Implications for Dosing and Labeling*.

597

598 FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and
599 Research, guidance for industry, *Drug Metabolism/Drug Interaction Studies in the Drug*
600 *Development Process: Studies in Vitro*.

601

602 FDA, Center for Drug Evaluation and Research and Center for Biologics Evaluation and
603 Research, guidance for industry, *Special Protocol Assessment*.

604

605 FDA, Center for Drug Evaluation and Research, draft guidance for industry, *Smallpox (Variola)*
606 *Infection: Developing Drugs for Treatment or Prevention*.

607

608 Leffel, E.K. and Pih, L.M. (2006), Anthrax. In Swarengen, J.R. (Ed.). Biodefense: Research
609 Methodology and Animal Models. (pp. 77-93). Boca Raton, FL: CRC Press.

610

611 USDA Animal Welfare Act, Public Law 89-544, as amended, 7 U.S.C. 2131 *et.seq.* (accessible
612 at <http://www.nal.usda.gov/awic/legislat/awa.htm>).

613

614 U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and
615 National Institute of Health, *Biosafety in Microbiological and Biomedical Laboratories (BMBL)*,
616 5th Edition, (Washington, DC: U.S. Government Printing Office, 2007): (accessible at
617 <http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm>).

618

619 *WHO guidelines on nonclinical evaluation of vaccines*, Geneva, World Health Organization,
620 2005 (WHO Technical Report Series, No. 927, Annex 1) (accessible at
621 http://www.who.int/biologicals/publications/trs/areas/vaccines/nonclinical_evaluation/en/).

622

REFERENCES